Report on Mishchencko et. al.

A statistical model describes calcium sensitive fluorescence dynamics in a small neural network. It is assumed that the calcium intake of a neuron follows a simple stochastic dynamics whose mean involves exponential decay at a rate which is neuron dependent, on top of fixed increments at spiking times. The calcium intake is itself observed through a noisy mechanism which is modeled as Gaussian with mean and variance non-linear functions of the true value. Neural firing is assumed to be a function of a base rate together with the weighted sum of the inputs from other neurons fed into a non-linear function, which defines the probability of firing. The main goal of this paper is to estimate the weights on the inputs from other neurons in the hope that this can provide insight into the actual synaptic connections between the neurons. This is done in a Bayesian framework where the prior on weights is intended to induce sparseness.

This is an interesting paper and the approach is novel and definitely worthy of publication. The statistical model is well defined and described very clearly. It is addressing a real scientific question of primary interest with novel methodological tools and is a perfect fit for AOAS. I would recommend a minor revision based on the following comments.

1. The statistical model has many layers and lots of parameters. The estimation of the weights is highly sensitive to proper estimation of other parameters as well as the inference on the hidden variables - i.e. the spikes. I think it would be interesting to have a short study of the robustness of weight estimation in the regime of full observations - i.e. the spikes are known. Here one could study the effects of *indirect connections* (are weights assigned between neurons that have no real synaptic connection), after all the weights are simply based on regressions.

   How does the level of connectivity affect the estimation. Do more connections make it less identifiable?

2. A graphic representation for a small network as in figure 1, which shows the existing connections vs. the inferred ones. I think you only show the inferred ones.

   In this context it may be of interest just to see which synapses were found to be present ignoring their weights.

   Also in reporting your results, maybe in addition to correlation you want to show some hamming distance between detected synapses and true synapses?

3. The main engine of the approach is in fact work done in another paper (Vogelstein et. al. (2009) by these authors and others, which describes an EM based approach to inferring spike trains (ignoring inputs from other neurons). I think that for completeness the main ingredients of the inference for the spikes and the other nuisance parameters should be included here. No need to deal with the super-resolution issues, but the basic particle filter would be useful to see in the current paper (and the notation in the current paper is much more pleasant to the eye...) In this context I have a few more specific comments:

   (a) In equation (7) it is not Q but the integrand of Q you are decomposing.

(b) In equation (10) you talk about the joint weight of a pair of particles. As far as I can see in (Vogelstein et. al. (2009) you have weights of individual particles. That should be clarified.

(c) At first glance the extraction of spikes from the noisy fluorescent signal seems like magic especially relative to the Weiner filter. However upon further thought I realized that because of the specific calcium dynamics the signal for a given neuron (modulo noise) is a superposition of exponentially decaying responses of fixed size and fixed decay rate (at unknown locations and of unknown number). The size and decay rate are estimated as well. Thus you are doing a smoothing operation with a constrained family of functions which of course makes the problem much more manageable. This may be worth mentioning. It is also related to the BARS method for fitting data due to Kass and collaborators.

4. It seems that ultimately the complicated Block Gibbs simulation of spikes is unnecessary. I would therefore take out that whole discussion in section (2.4) and proceed directly to 2.4.1. My intuition is that if you really need to rely on simulating the spikes based on their interactions you would be in trouble for estimating the weights. The basic data should provide a good indication of where the spikes are.